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Review

Critical Considerations for Mesenchymal Stem Cell-based Therapies in Osteoarthritis and Spinal Cord Injury: A Narrative Review

Shaolong Li[1#], Chenxi Zhao[1#], Wei Wang[1], Wenhan An[2], Xinyu Liu[3], Hengxing Zhou[1], Xiaohong Kong[1], David D. Dean[4,5], Shiqing Feng[1,6,7*], Xiao-Dong Chen[4,8*]

[1]Department of Orthopaedics, Qilu Hospital, Shandong University Centre for Orthopaedics, Advanced Medical Research Institute, Cheeloo College of Medicine, Shandong University, Shandong, China; [2]Department of Rehabilitation, The Second Hospital of Shandong University, Shandong, China; [3]Department of Orthopaedic Surgery, Qilu Hospital, Shandong University, Shandong, China; [4]Department of Comprehensive Dentistry, School of Dentistry, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, USA; [5]Department of Biomedical Engineering, University of Texas at San Antonio, San Antonio, TX 78249, USA; [6]The Second Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China; [7]Department of Orthopaedics, Tianjin Medical University General Hospital, International Science and Technology Cooperation Base of Spinal Cord Injury, Tianjin Key Laboratory of Spine and Spinal Cord, Tianjin, China; [8]Research Service, South Texas Veterans Health Care System, San Antonio, TX 78229, USA.

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ABSTRACT: Mesenchymal stem cells (MSCs) have been proposed as treatments for degenerative diseases, but clinical outcomes have been inconsistent. Here, we reviewed the ClinicalTrials.gov database and identified ~1,600 trials associated with MSC-based therapies; osteoarthritis (OA) and spinal cord injury (SCI) were most frequently investigated, but the reporting of results was consistently low (<7%). We next searched the PubMed database and identified 26 OA and 16 SCI published trials, which included studies from one or both databases. Our analysis identified a common set of factors that influenced therapeutic efficacy in both diseases, including MSC source, donor type, dose/route & frequency of administration, and patient variation. Of these, three factors were significant for improving efficacy. *MSC quality* is affected by age of the donor, and this is especially important when treating older OA patients with autologous MSCs. *Phase of the disease* is important, and both OA and SCI may benefit from early treatment, since MSCs can ameliorate inflammation and initiate tissue repair. *MSC source* is critical as allogenic MSCs are no longer considered "immune privileged", and autologous cells can differentiate and repair damaged tissue without immune interference. The results of this narrative literature review suggest that establishing a personal autologous MSC bank may be an essential component for achieving success with MSC-based therapies, since MSCs from this repository could be deployed early, ameliorate inflammation, and initiate repair of damaged tissues.

Keywords: Stem cell efficacy, clinical trials, osteoarthritis, spinal cord injury, critical influences

1. Introduction

Although it has been about 50 years since A.J. Friedenstein discovered bone marrow-derived mesenchymal stem cells (BM-MSCs) or BM stromal stem cells, that can differentiate into multiple cell lineages [1, 2], these cells are still a long way from being used in the clinic to treat degenerative diseases. By 2006, nearly 30

***Correspondence should be addressed to:** Dr. Xiao-Dong Chen, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229, USA. Email: chenx4@uthscsa.edu; Dr. Shiqing Feng, Qilu Hospital of Shandong University, Jinan, China. Email: shiqingfeng@sdu.edu.cn. # These authors contributed equally to this work and shared first authorship.

years after their identification, the International Society for Cellular Therapy (ISCT) proposed and published the following four minimal criteria for defining MSCs: 1) attachment to tissue culture plastic (TCP) surfaces, 2) expression of the following cell surface biomarkers: CD105, CD90, and CD73, 3) lack of expression of the following cell surface antigens: CD45, CD19, CD14, CD11b, CD34, CD79α, and HLA-DR, and 4) capacity to differentiate into osteoblasts, chondrocytes, and adipocytes (i.e. tri-lineage differentiation potential) [3]. Since the promulgation of these guidelines, MSCs have been found to display properties beyond their "cell reservoir" function and behave as a "drug store" [4]. Specifically, MSCs can secrete growth factors or cytokines, as well as extracellular vesicles, which have potent autocrine and paracrine effects on nearby cells, reactivating the quiescent endogenous stem cell population, inhibiting apoptosis and inflammation, and restoring the aging microenvironment [5-7]. In addition, MSCs also exert direct effects on target cells through donation or transfer of mitochondria, which prevent apoptosis and reverse metabolic damage [8], and modulate the immune response by decreasing inflammation and preventing scar formation.

Table 1. Profile of Diseases/Medical Conditions Studied in Three or More Clinical Trials Using MSCs.

#	Disease	No. Clinical Trials	% of All Trials	% Completed	% Reporting Results
1	**Osteoarthritis**	**64**	**9.0%**	**69%**	**9%**
2	COVID-19, ARDS	35	5.0%	66%	17%
3	**Spinal Cord Injury**	**28**	**4.0%**	**43%**	**7%**
4	Multiple Sclerosis	26	3.6%	85%	15%
5	Graft vs. Host Disease	24	3.3%	66%	4%
6	Crohn's Disease	20	2.8%	55%	0%
7	Myocardial Infarction	19	2.7%	84%	20%
8	Stroke, Ischemic	19	2.7%	53%	5%
9	Cirrhosis, Liver	19	2.7%	63%	0%
10	Heart Failure	18	2.5%	77%	22%
11	Amyotrophic Lateral Sclerosis	18	2.5%	72%	11%
12	Ischemia, Peripheral Artery	15	2.1%	73%	0%
13	Cardiomyopathy	15	2.1%	80%	20%
14	Diabetic Foot, Ischemia	15	2.1%	80%	0%
15	Limb-threatening Ischemia	13	1.8%	77%	0%
16	Diabetes, Type 2	12	1.6%	75%	8%
17	Kidney Disease, Chronic	11	1.5%	73%	9%
18	Rheumatoid Arthritis	11	1.5%	54%	9%
19	Erectile Dysfunction	10	1.4%	50%	0%
20	Cartilage Injury	10	1.4%	70%	10%
21	Retinal Degeneration, Retinitis	9	1.3%	66%	11%
22	Fistula, Anal/Perianal	9	1.3%	44%	0%
23	Retinitis Pigmentosa	8	1.1%	63%	0%
24	Diabetes, Type 1	7	1.0%	71%	0%
25	Parkinson's Disease	7	1.0%	57%	14%
26	Intervertebral Disc Disease	7	1.0%	71%	29%
27	Incontinence	6	0.8%	83%	0%
28	Ulcer, Chronic	5	0.7%	80%	0%
29	Transplantation, Renal	5	0.6%	80%	20%
30	Fracture, Nonunion	4	0.6%	100%	0%
31	Pancreatitis	4	0.5%	50%	0%
32	Osteonecrosis, Femoral head	3	0.4%	100%	0%
33	Shock, Septic	3	0.4%	66%	0%
34	Fracture, Tibial	3	0.4%	100%	0%
Total # of Clinical Trials (out of 718) with ≥3 Studies		**482**			
Average % Completed				**70.5%**	
Average % Reporting Results					**7.1%**
Data collected 11/12/2025					

Currently, BM-MSCs are considered the 'gold standard' for cell-based therapies [9, 10]. Since adult BM only contains a small number of MSCs (~ 0.001%)[11, 12], these cells must be expanded *in vitro* to obtain enough stem cells for basic research or clinical applications. However, during routine culture on TCP surfaces, MSCs lose their multipotentiality and ability to self-renew, while the number of senescent cells increases [13-15], hindering efforts to obtain large numbers of high-quality MSCs. Our research labs have had an interest in understanding how the microenvironment controls MSC fate and have obtained evidence suggesting that biochemical, biomechanical, and architectural cues in the extracellular matrix (ECM), which is a major component of the stem cell niche, play a critical role in retaining MSC self-renewal and governing MSC differentiation [16-18]. Our hypothesis for this narrative review is that the wide variety of MSC culture conditions, sources of tissues (e.g., bone marrow, adipose, umbilical cord, etc.), and types of donors (i.e., allogenic versus autologous & young versus old) alter the quantity and quality of cells used in MSC-based therapies and result in variable clinical outcomes.

2. Method of Approach (Search Strategy)

To test our hypothesis, we reviewed all clinical trials of MSC-based therapies archived in the ClinicalTrials database and initially identified 1622 studies that used MSCs, after excluding studies that had been previously terminated, suspended, withdrawn, or required an invitation to participate, based on the strategy shown in Figure 1. When the search was further refined to only include those studies that were interventional and employed subjects of both sexes and all ages, a total of 718 studies remained. When further segregated by tissue source, 607 (85%) of the 718 studies used MSCs derived from bone marrow (BM: 214 studies), adipose tissue (AD: 160 studies), and umbilical cord/Wharton's jelly (UC/WJ: 233 studies), which were used in the treatment of 108 different diseases. Next, we tabulated information on the top 34 diseases (Table 1), where ⩾3 studies (trials) were reported; in this group, 70% were complete, but only 7% reported results. Furthermore, we noted that osteoarthritis (OA) (9% of all trials) and spinal cord injury (SCI) (4% of all trials) were the most studied diseases at positions 1 and 3, respectively. COVID-19, a recent pandemic disease, was excluded from this review since we focused on common diseases where a strong rationale for the use of MSC-based therapy had been previously demonstrated. Interestingly, it was noted that only 9% and 7% of the OA and SCI clinical trials, respectively, had reported results in the ClinicalTrials database (Table 1).

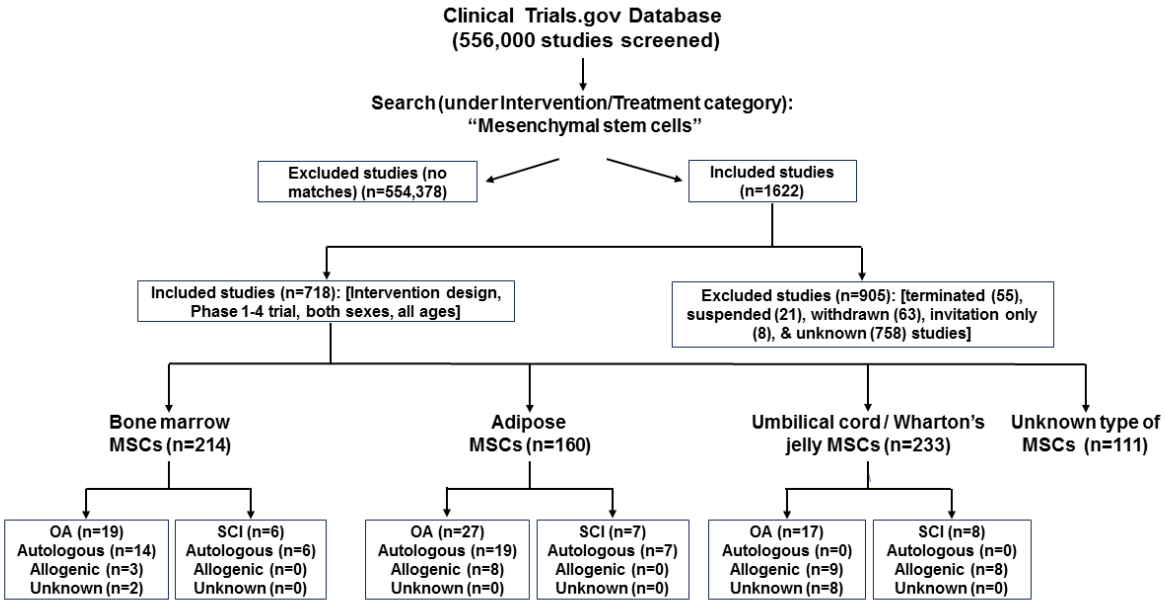

Figure 1. Search strategy for MSC trials across diseases. An overview of the strategy used to search the ClinicalTrials.gov database to identify clinical studies that used MSCs from bone marrow, adipose tissue, or umbilical cord (UC)/Wharton's jelly to treat a variety of over 100 diseases.

To obtain a more complete set of data, we performed a second search using the PubMed Central (PMC) database for OA and SCI studies and used the same search terms as before (see Table 2). By combining the results

of both searches (ClinicalTrials & PMC), we identified 26 clinical trials for OA and 16 clinical trials for SCI which were published in peer-reviewed literature and contained informative results (Tables 3 & 4).

In this narrative review, we provide a comprehensive overview of factors that might influence the efficacy of stem cell treatment, including MSC donor type (e.g., allogenic vs autologous MSCs), donor age (e.g. young vs. old), tissue source (e.g, BM-, AD-, and UC-MSCs), freshly isolated BM aspirate concentrate (BMAC) or adipose-derived stromal vascular fraction (SVF) vs cultured MSCs, route, dose, and frequency of MSC administration (e.g, local vs systemic, number of cells, and single vs multiple injections), and variation in the recipient/patient population (e.g., age, BMI, stage of disease, prior/current medication use, complications, and short vs long-term follow up).

Table 2. Strategy Used to Conduct Searches in PubMed.

Osteoarthritis	Spinal Cord Injury
"Mesenchymal stem cells"	"Mesenchymal stem cells"
AND	AND
"Bone marrow" OR "Adipose tissue" OR "Umbilical cord/Wharton's jelly"	"Bone marrow" OR "Adipose tissue" OR "Umbilical cord/Wharton's jelly"
AND	AND
"Osteoarthritis"	"Spinal cord injury"
AND	AND
"Autologous" OR "Allogenic"	"Autologous" OR "Allogenic"

3. Why is OA the most frequently studied disease using MSC-based therapy?

According to the Global Burden of Disease (GBD), produced by the Institute for Health Metrics and Evaluation, OA is ranked as one of the top diseases that has a significant impact on healthcare costs and quality of life [19]. Currently OA affects 7.6% of the global population with 240 million OA patients >60 years of age [20]. Between 1990 and 2017, the annual incidence of new OA cases, confirmed by imaging studies, was as high as 15 million [21]. Recently, it was found that over half of new cases of OA were early onset and developed before the age of 55 [19]. Consequently, we are facing a huge, continuously growing population of OA patients that is expanding in parallel with global aging [22].

OA is characterized by synovial inflammation and destruction of articular cartilage, which frequently results in knee pain, stiffness, and loss of mobility [23]. Conventional therapies for OA include various drugs as well as non-pharmacological interventions that emphasize weight loss, exercise, physical therapy, and surgery [24]. Drug therapies include oral medications [e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and chondroprotective agents] and intra-articular injections [e.g. corticosteroids, hyaluronic acid (HA); platelet-rich plasma (PRP)], while surgical treatments include arthroscopy (e.g. washing out the joint space and/or repairing joint structures via minimally invasive procedures), open surgeries to repair extensively damaged cartilage, and total or partial joint arthroplasties for end-stage OA [24, 25]. However, arthroplasty has the potential to cause a variety of serious complications [26], such as prosthetic joint infection [27], periprosthetic fracture [28], and pulmonary embolism [29]. Taken together, these conventional therapies can manage the symptoms of OA, but not cure the disease, and often have adverse side effects.

The early stages of OA are associated with the production of TNF-α and IL-1β [30-33], where TNF-α is mainly involved in upregulating inflammation and IL-1β stimulates cartilage degradation[32]. When IL-1β secretion is upregulated, the production of matrix metalloproteinases (MMPs) is increased, while synthesis of extracellular matrix (ECM) is decreased [34, 35]. These events occur through activation of the MAPK and NF-κB signaling pathways and result in loss of articular cartilage [30, 35].

The rationale for using MSCs to treat OA is based on three of their main properties. First, MSCs are able to reduce the production of pro-inflammatory factors by regulating macrophage differentiation or promoting the transformation of macrophages from the M1 to M2 state [36], affecting dendritic cell (DC) phenotype, inhibiting natural killer cell (NKC) proliferation, and inducing lymphocyte apoptosis [37]. In the case of OA, MSCs reduce inflammation by producing exosomes that inhibit the activation of NLRP3 (NLR family pyrin domain containing 3), a crucial intracellular sensor in the innate immune system involved in forming the NLRP3 inflammasome, and induce macrophage polarization to the M2 state [38, 39]. Second, MSC-derived exosomes not only promote the synthesis of type 2 collagen but also inhibit IL-1β-induced MMP-13 production resulting in

the attenuation of ECM degradation [38, 40-43]. Third, MSCs can also differentiate into chondrocytes in response to TGF-β that promotes the expression of SOX9, a crucial transcription factor for cartilage formation via Smad3 signaling [44-46].

Moreover, OA is an ideal candidate for MSC-based therapy since articular cartilage can be accessed easily by local injection, which is a safer (lower immunogenicity) route than systemic administration, and permits a higher concentration of the cells to be directly deposited at the lesion site. In addition, treatment efficacy can be directly monitored by a variety of imaging techniques (CT, MRI) that facilitate less biased long-term follow up studies [47, 48]. However, at the present time, there is no widely accepted procedure for treating OA with MSCs and clinical trial results vary substantially due to differences in procedures and assessment methodologies [49].

Table 3. Clinical Trials Using MSCs to Treat Osteoarthritis.

#	NCT #	Pub	#Patients/ Aver. Age	K-L grade	Cell source / Dose	Route/Dose Frequency	Main results	Outcome	Ref
1	Unregistered	2014	18 / 63yrs	3.0-4.0	Auto AD-MSC /1-10 x10^7cells	I.A /once	VAS and WOMAC scores: All groups showed improvement; only the high-dose was statistically significant. Only MRI showed a reduction in defect area in the high dose group; No other changes by imaging or arthroscopy were significant.	U (low/med dose) S (high dose)	[89]
2	NCT01586312	2015	30 / 57yrs	2.0-4.0	Allo BM-MSC (young donor) / 4×10^7 cells	I.A/once	VAS, WOMAC and LEQUESNE scores: All groups showed improvement, but only the experimental group was significant. By imaging, only pool cart index (PCI) of both groups decreased; PCI change in the experimental group was statistically significant at 12 months.	S	[184]
3	Unregistered	2017	7 / 59yrs	3.0	Allo UC-MSC +HA / 5×10^6 cells/ml	I.A. (0.5ml/cm 2) / once	VAS and IKDC scores: OA was significantly improved after transplantation; results were statistically significant. By arthroscopy, mature repair tissue observed	S	[185]
4	NCT02123368	2016	25 / 60yrs	2.0-4.0	Auto BM-MSC /1-10 x10^7cells	I.A /once	VAS and WOMAC scores: Progressive improvement in the experimental group and deterioration in the control group. Significant change in VAS and WOMAC scores between low-dose & high-dose and control groups.	U	[186]
5	NCT01931007	2017	25 / 60yrs	1.0-3.0	Auto BM-MSC (BMAC+PP P) / N.R.	I.A./once	ICOAP and VAS scores: all improvements were significant in each group; changes between groups were not statistically significant	U	[187]
6	NCT01088191	2017	17 / 26yrs	N.R.	Allo BM-MSC (young donor) / 7.5×10^7 cells	I.A/once	KOOS and SF36 scores were both improved. Improvement in the experimental group was significant & changes between groups were statistically significant. MRI: No significant change in tibial cartilage volume; dilation of tibial cartilage in the experimental group was significantly reduced & changes between groups were significant; knee joint width of the experimental group increased & changes between groups were significant	S	[188]
7	Unregistered	2018	18 / 57yrs	2.0-4.0	Auto BM-MSC +PRP / 4×10^7 cells	I.A./once	KOOS score: no significant changes between groups (MSCs alone vs. MSCs + PRP)	U	[189]
8	NCT01504464	2018	47 / 52yrs	2.0-4.0	Auto BM-MSC / 4x10^7cells	I.A./once	Change in walking distance, painless walking distance, VAS, standing time, WOMAC, & joint curvature:	U	[190]

							Only change in painless walking distance and WOMAC were significant.		
9	NCT02162693	2019	53 / 55yrs	1.0-3.0	Auto AD-MSC / $5x10^7$cells	I.A./once	VAS score and SF36 score: changes between groups were statistically significant. WOMAC score: Changes between groups were not statistically significant. MRI: Cartilage volume of the experimental group increased, while control group decreased.	S	[191]
10	NCT02658344	2019	24 / 62yrs	2.0-4.0	Auto AD-MSC / $1x10^8$cells	I.A./once	WOMAC, VAS and KOOS scores: Changes between groups were statistically significant. Imaging: no significant improvement observed	U	[192]
11	NCT02580695	2019	26 / 56yrs	1.0-3.0	Allo UC-MSC / $2x10^7$ cells	I.A./twice (repeat @ week 26)	WOMAC and VAS: Changes between groups were improved and statistically significant. MRI: no significant improvement observed	U	[78]
12	NCT02351011	2019	12 / 56yrs	3.0	Auto BM-MSC / 1-50 $\times10^6$ cells	I.A /once	KOOS, WOMAC scores: KOOS pain, QoL, and WOMAC stiffness scores showed statistically significant changes. Changes in WOMAC function/pain and KOOS motor changes were not significant. No improvement seen on MRI.	U	[193]
13	Iranian registry of clinical trials	2019	20 / 35-75yrs	2.0-4.0	Allo UC-MSC / 5-6 $\times10^7$ cells	I.A./once	VAS and KOOS scores: Scores were not significantly improved between groups. ROM (hyperextension, hyperflexion & total curvature): Changes in the experimental group, but not control group, were significant. Changes between groups were statistically significant.	U	[194]
14	Unregistered	2019	25 / 60yrs	1.0-3.0	Auto BM-MSC (BMAC+PPP) / N.R.	I.A./once	ICOAP, VAS score, pain measurement, and exercise level: Changes between groups were not statistically significant. K-L classification and MRI: no improvement observed.	U	[195]
15	NCT02365142	2020	60 / 33-70yrs	2.0-4.0	Auto BM-MSC/ 1×10^8 cells	I.A. / once	VAS and WOMAC scores: Changes between groups were not statistically significant. MRI: no significant improvement	U	[196]
16	Unregistered	2020	47 / 55yrs	1.0-4.0	Auto BM-MSC +PRP / 4×10^7 cells	I.A. / once	KOOS score: Improvement in MSC group and MSC＋PRP group was significant. Changes between groups were not compared. No significant difference in ROM among groups. No imaging studies performed.	U	[197]
17	NCT02726945	2020	39 / 59yrs	2.0-3.0	Auto AD-MSC (SVF) / $1.5\text{-}3.0\times10^7$ cells	I.A. / once	WOMAC: Changes between groups were statistically significant. MRI: no significant improvement	U	[198]
18	NCT02641860	2020	22 / 58yrs	2.0-4.0	Allo AD-MSC (unknown donor age) /1, 2 & 5 $\times10^7$ cells	I.A. / once	VAS, WOMAC and SF36 scores: all improvements were significant in each group; changes within the group were significant, with no comparison between groups. MRI: Changes were inconsistent.	U	[199]
19	Unregistered	2021	60 / 61yrs	1.0-4.0	Auto BM-MSC (BMAC) / N.R.	Subchondral bone or I.A. / once	VAS, KL, & synovitis scores, and "knee joint survival rate": Subchondral injection was better than I.A.; changes between groups were statistically significant.	S	[69]
20	NCT03990805	2023	252 / 64yrs	3.0	Auto AD-MSC / $1x10^8$ cells	I.A. / once	VAS and WOMAC scores were significantly better in treated subjects compared to controls after 6 months. Radiologic outcomes,	U	[200]

							including MRI, were not different between treated and control groups.		
21	NCT03818737	2023	475 / 58yrs	2.0-4.0	a) Auto BM-MSCs (BMAC) /N.R. b) Auto-AD-MSCs (SVF) N.R. c) Allo-UC-MSCs /N.R. d) Steroid	I.A. / once	VAS and KOOS scores for subjects in the 3 orthobiologic groups were statistically equivalent at 12 months post-injection; subjects in the steroid group were equivalent to those in the orthobiologic groups. Moreover, none of the groups showed any improvement in their MRI scans when compared to baseline (pre-op).	U	[60]
22	NCT04043819	2024	29 / 66yrs	2.9	Auto AD-MSC (SVF) / 2-10×10^6 cells	I.A. / once	KOOS demonstrated notable improvements at 84 days and 12 months after treatment. No imaging studies were conducted. No severe adverse events noted. First US FDA approved clinical trial of autologous SVF product manufactured in an FDA compliant cGMP facility.	U	[201]
23	Unregistered	2024	29 / 58yrs	3.0-4.0	Auto BM-MSC (BMAC) / N.R.	I.A. / once	IKDC and WOMAC scores showed significant improvement from year 2 through year 4. KL scores improved significantly with treatment. Pre- and Post-operative MRI scans were not performed; however, the length of follow up (4 years) was exceptionally long.	U	[61]
24	NCT03955497	2024	45 / 54yrs	1.0-3.0	Auto-AD-MSCs / 5X10^7 cells	I.A. / once	Prior to AD-MSC treatment, MRI images showed presence of inflammation and loss of cartilage; 12 months after treatment, all signs of inflammation and cartilage loss were gone. These results were confirmed by arthroscopy. VAS and WOMAC assessments were performed at 0, 6, 12, and 24 months; the results showed no improvement in VAS but a reduction in WOMAC at 24 months. Importantly, proliferation and colony forming efficiency of AD-MSCs from patients showing the most improvement also had lower amounts of senescent cells and intracellular reactive oxygen species (ROS) production.	S	[59]
25	NCT04240873	2025	20 / 68yrs	2.0-4.0	Allo BM-MSC (young donors/20-55yrs) / 1x10^8 cells	I.A. / once	VAS, WOMAC, and KOOS: significant improvement in WOMAC and KOOS pain scores between baseline and 12months; significant improvement in controls not observed. T2 MRI showed a significant preventive effect of MSCs on cartilage degeneration.	S	[23]
26	Unregistered	2025	30 / 63yrs	2.0-3.0	Allo UC-MSC / 5 x 10^6 cells	I.A. / once	WOMAC and numerical rating score (NRS), and SF-36 profile were significantly improved with treatment after 12 months; no severe adverse events noted. MRI scores between treated and untreated were not different.	U	[202]

Twenty-six clinical trials were identified and evaluated the safety and efficacy of MSCs for treating OA. Factors that were followed in all of the studies included source of the cells, dose and frequency of transplantation, route of administration and methods used to assess each patient's progress (visual analogue score [VAS], Western Ontario and McMaster Universities [WOMAC] score, short form 36 to assess quality of life, Knee Injury and Osteoarthritis Outcome Score [KOOS], imaging [x-ray; Kellgren-Lawrence scale, MRI, and arthroscopic changes). Outcome of treatment was measured by improvement in cartilage lesion based on imaging data (=Satisfactory outcome), versus no objective evidence of tissue repair based on imaging analysis or not provided or performed in the study (=Unsatisfactory outcome).
Abbreviations used in the table:

AD: Adipose tissue-derived; **Allo**: Allogeneic; **Auto**: Autologous; **BMAC**: Bone marrow aspirate concentrate; **BM**: Bone marrow-derived; **HA**: Hyaluronic acid; **I.A.**: Intra-articular injection; **K-L**: Kellgren-Lawrence grade; NCT # = ClinicalTrials.gov ID; **N.R.**: Not reported; **PPP:** Platelet poor plasma; **PRP**: Platelet rich plasma; **Pub** = Publication date; **SVF**: Stromal vascular fraction; **UC**: umbilical cord-derived

4. Factors that Influence the Clinical Results of MSC Treatment in OA

As shown in Table 3, 26 clinical trials were identified from peer reviewed publications that evaluated the safety and efficacy of MSCs for the treatment of OA. Factors that potentially affected the results are indicated in the table, including the source of cells, dose and frequency of transplantation, route of cell administration, and methods used to assess each patient's progress. The results for each of the trials included one or more of the following assessment tools/questionnaires: Visual Analogue Score (VAS) [50], Western Ontario and McMaster Universities (WOMAC) score [51], health-related quality-of-life measure Short Form 36 (SF36) [52], Knee Injury and Osteoarthritis Outcome Score (KOOS) [53], imaging (x-ray, Kellgren & Lawrence scale [54]，and/or MRI [55]), and arthroscopic changes.

An overall analysis of the results shows that, although the experimental conditions of each clinical trial are different, almost all of them demonstrate that the treatment was safe and produced symptomatic improvement based on VAS, WOMAC, SF36, and KOOS scores which are *subjective* measures. In contrast, we have found that although the clinical diagnosis of OA is primarily based on symptoms, imaging studies provide a more *objective set of criteria* for determining cartilage loss, joint changes, etc. [56]. Moreover, studies have shown that the diagnostic value of symptoms in *early* OA is limited, while MRI is sensitive and able to detect early structural changes [57]. Thus, in this review, a "satisfactory" outcome was defined by an improvement in a cartilage lesion with treatment, based on imaging studies (e.g. MRI and arthroscopy), versus an "unsatisfactory" outcome where there was no objective evidence of tissue repair based on an imaging analysis, or which was not provided or performed in the study.

4.1 Influence of cell source

Bone marrow- (BM-), adipose tissue- (AD-), and umbilical cord- (UC-) derived MSCs have their own unique characteristics in terms of their capacity for proliferation, differentiation, production of anti-inflammatory factors, and immune modulation. To demonstrate whether these differences have an effect on clinical outcome (i.e., one source of MSCs has a greater ability to ameliorate OA than the other two), we analyzed the studies listed in Table 3 and found that among the 28 clinical trials [n.b., one publication (#21) used 3 types/sources of cells], 14 used BM-MSCs with satisfactory results in 4 (4/14), 9 selected AD-MSCs with satisfactory results in 3 (3/9), and 5 used UC-MSCs with satisfactory results in 1 (1/5). Since these differences were relatively small, we then divided the studies based on cell origin (autologous vs allogeneic). By this approach, we were surprised to find that 19 studies used autologous cells, but only 4 (4/19; 21%) produced satisfactory results, while 9 studies used allogenic cells and in 4 (4/9; 44%) the results were satisfactory. Although the number of studies is small, such a large difference caught our attention. To explore why autologous cell transplantation produced relatively poor results, we analyzed the baseline characteristics of the patients in each study and found that autologous cells were mainly provided by older adults, while allogenic cells were obtained from young donors (the published studies listed in Table 3 did not specify an exact age, only that the allogenic donors were young). As mentioned above, it is well known that patient age can have a significant effect on MSC quality [58]. This notion is clearly supported by studies #7 and #24 (NCT03955497) in Table 3, which suggest that a higher number of colony forming units-fibroblast (CFU-F) generated by autologous BM-MSCs or AD-MSCs was associated with an improvement in response to MSC treatment [59], as well as fewer senescent cells and lower amounts of intracellular reactive oxygen species [59]. Unfortunately, very few clinical investigations evaluate the stemness of autologous MSCs before administration. We strongly suggest that a correlation between the quality of autologous MSCs and clinical efficacy needs to be demonstrated.

Interestingly, 7 studies (#5, 14, 17, 19, 21-23) listed in Table 3 used BMAC or adipose-derived SVF without culture expansion and only 1 of these studies elicited a "satisfactory" response. Mautner et al (#21) compared BMAC-, SVF- and UC-derived MSCs vs corticosteroid injections for knee OA in 480 patients. After 1 year, there was no significant difference in effectiveness between the groups [60]. Recently, Pabinger et al (#23) reported that the injection of BMAC into the knees of 37 subjects with Kellgren-Lawrence grade III and IV OA and a 4-year follow up showed a significant amount of improvement based on International Knee Documentation Committee (IKDC) and WOMAC scores, which was not supported by MRI studies [61]. It should be noted that such "Minimal Manipulation of Human Cells", as is performed in the preparation of BMAC and SVF, has been reported to be generally unsuitable for MSC-based therapies due to the extremely low number of stem cells [62].

Furthermore, many of these primary cells may be quiescent. Increasing the number of cells and reactivating them are necessary steps to enhance clinical efficacy.

Recently, we reported that aging AD-MSCs could be rescued by culture on a native decellularized ECM synthesized by human amniotic fluid-derived pluripotent stem cells (AFCs) [63]. Culture on this "young" microenvironment (i.e., AFC-ECM) was associated with a remarkable up-regulation of intracellular CD74 in the cells, compared to culture on regular TCP, which subsequently triggered activation of the phosphoinositol-3-kinase (PI3K) pathway as a key modulator of cell survival and suppression of cellular senescence and apoptosis. Moreover, AD-MSCs maintained on AFC-ECM increased their expression of HLA-DR and stimulated T cell activity [63]. These findings challenge the long-held view that MSCs do not express HLA-DR and strongly suggest that failure to express HLA-DR is due to culture on an artificial substrate (i.e., regular TCP). Since the matrix proteins found in AFC-ECM consist of ~39% collagens and ~49% glycoproteins [64], simulating the physiological microenvironment *in vivo*, the transplanted MSCs may be exposed to these ECM proteins *in vivo* and likely induce the expression of HLA-DR. In support of this hypothesis, it has been shown that transplanted allogenic MSCs are more rapidly rejected in previously sensitized animals, with most cells killed within 48 hours after systemic infusion [65, 66]. This observation is consistent with the fact that very few studies show newly formed tissue *directly generated* by the transplanted allogenic MSCs *in vivo* [67], as opposed to the transplanted cells secreting trophic factors which reactivate the quiescent endogenous stem cell population [68]. As we make progress in pursuing MSC-based personalized therapies, researchers in the future may compare "autologous rejuvenated MSCs" from old adults with allogenic MSCs from young donors and perhaps demonstrate the validity of the approach.

4.2 Influence of transplantation route on the efficacy of MSC treatment of OA

As can be seen in Table 3, trial #19 compared intra-articular vs subchondral injection on the same individual in over 60 patients with bilateral OA [69]: one knee received an intra-articular injection while the contralateral knee received a subchondral injection. After 2 years, an MRI at follow up revealed that there was significant improvement in the knee treated with a subchondral injection as compared to the contralateral knee that received an intra-articular injection; as a result, the incidence of total knee arthroplasty (TKA) in subjects receiving the subchondral injection was significantly less than in those receiving an intra-articular injection (1.3% vs 4.6% per knee/year, respectively). Over a total of 15 years of follow-up, 12 (20%) of the 60 subjects that were re-treated with subchondral injection subsequently underwent TKA, while 42 (70%) of the 60 subjects that were re-treated with intra-articular injection later underwent TKA. These results were confirmed by the same group in an identical repeat study on 140 patients [70]. Recently, a systematic review confirmed the safety and efficacy of subchondral injection [71], while another report compared three different methods of transplantation (i.e., intra-articular, subchondral, and intra-articular with a scaffold) and concluded that subchondral injection was the most effective approach [72].

The attention paid to the subchondral transplantation method may be related to the hypothesis that OA lesions originate in the subchondral bone [73], as studies have shown the presence of increased levels of IL-1β, IL-6, and leukotrienes that may be responsible for the etiology of OA in the subchondral bone[74, 75]. However, a specific mechanism for the effect of subchondral injection of MSCs for the treatment of OA is still unclear. Although there are few studies on subchondral injection of MSCs, the existing clinical trials show that subchondral injection is a promising treatment, and researchers need to further explore its therapeutic mechanism and potential clinical effects.

4.3 Influence of transplantation frequency on treatment success in OA

Since OA is a chronic disease, the frequency of transplantation may have an impact on therapeutic efficacy. Although this is widely believed to be true [37, 76, 77], there was only one report (#11 in Table 3) which directly addressed the effect of repeat transplantation in knee OA. In this report, 10 subjects received only one dose of UC-MSCs (2×10^7), while a second group of 10 subjects received the first dose followed by a second dose 6 months later [78]. At the 12 month-follow-up, subjects who received 2 injections were significantly improved, based on WOMAC scores (a subjective measure), versus subjects who only received 1 injection. However, there were no differences in MRI scores (an objective measure) between the two groups. Since reports in the preclinical literature indicate that a range of transplantation frequencies provide improvement in OA symptoms [79], we carefully reviewed the clinical literature to determine if multiple transplants might be more effective than single transplants. Based on our objective criteria, it failed to support the idea that transplantation frequency has any effect on treatment success. Future clinical trials are needed to demonstrate if increased transplantation frequency has a positive effect on OA.

4.4 Individual variation in OA patients has a major influence on MSC treatment efficacy

The individual characteristics of each patient, including age, disease severity (e.g., Kellgren-Lawrence grade), prior medication usage, body mass index, and dose of transplanted cells may also influence clinical outcomes. As mentioned previously, age may have an effect on the quality of autologous cells and this has been confirmed previously in studies showing that autologous MSC transplantation in patients over the age of 60 is largely ineffective [80]. Moreover, the aged microenvironment in older patients may also impair the function of transplanted MSCs, which has been previously demonstrated in mice [58, 81]. Recently, a report by Sun et al (#24 in Table 3) suggested that inconsistent clinical outcomes of studies are correlated with differences in the quantity and quality of the injected autologous MSCs and that MSC properties such as proliferation and differentiation, CFU efficiency, cell senescence and production of reactive oxygen species (ROS) could be used for predicting clinical outcomes in autologous MSC-based therapy for knee OA. As an approach for improving clinical efficacy, we have previously proposed to rejuvenate autologous MSCs (especially from older patients) by culturing the cells on a young microenvironment and then standardize the quantity/quality of the cells prior to administration [58, 81].

Disease severity may also have an impact on the therapeutic efficacy of MSC transplantation, although no significant relationship has been found in the 26 clinical trials, which we have reviewed here. Interestingly, a 2016 meta-analysis showed that patients with knee Kellgren-Lawrence (K-L) grades of 1-2 (i.e., mild OA injury) displayed a significantly better response to MSC transplantation than patients with knee K-L grades of 3-4 (i.e., severe OA injury) [82]. Other studies have used the extent of injury (e.g. lesion size) to judge OA severity and found that MSC transplantation was ineffective in patients with lesions $>6cm^2$ [80]. Taken together, the evidence to date supports MSC transplantation being more suitable for patients with mild OA than for those with severe OA. With regard to severe OA patients, we speculate that disease-related degeneration of the microenvironment and large defects at the site of cartilage damage/injury may adversely affect MSC behavior/function. To solve this problem, scaffolds or delivery vehicles for carrying MSCs have been proposed to directly home to the defect site and ensure MSC survival and promote MSC differentiation. For example, hydrogels are routinely used as carriers and have many advantages since they can easily fill cartilage defects of various shapes and sizes and also reduce mechanical forces generated on the MSCs during injection (due to syringe needle flow) and thereby increase cell viability [83, 84]. In some of the newer hydrogels [85, 86], differentiation of MSCs into chondrocytes is promoted. These approaches suggest that MSCs delivered in carriers/scaffolds, which protect the cells and fill large cartilage defects, may be an effective way of treating severe OA.

Body mass index (BMI), a measure of obesity, is an important morbidity factor for OA. By analyzing the baseline characteristics of the patients in each clinical trial, we found that the average BMI for almost all clinical trials was in the "obese" or "overweight" range. Since the clinical trials that we reviewed here did not include non-obese patients as controls, we cannot determine if obesity had an impact on MSC treatment. However, AD-MSCs from obese patients often displayed functional impairment and a poor response when autologous AD-MSCs were transplanted for treatment of OA [87]. Although there is no additional evidence showing that standardized MSCs function differently when administered to patients with different BMIs, it is possible that MSC treatment of obese patients will remain suboptimal due to the more intense inflammatory environment found in these patients [88]. Of course, this conclusion needs to be researched further and supported by parallel controlled clinical trials in the future.

The effect of stem cell dose on the efficacy of MSC transplantation is somewhat supported by a number of parallel controlled clinical trials, but the conclusions are not uniform. Data from some trials have shown that a high dose of cells (1×10^8 cells), but not a low dose ($1.0\text{-}6.4\times10^7$), produces a significant improvement in OA symptoms after 6 months [89, 90], while after 12 months both doses appear to produce an improvement in symptoms with no significant differences [90, 91]. There is also a meta-analysis which failed to demonstrate a dose-response relationship between the number of MSCs transplanted and treatment outcome [82]. From the OA clinical trials that we reviewed (Table 3), the most common dose used for transplantation is $1-10\times10^7$ cells, but there is no correlation between transplantation dose and therapeutic effect. More parallel-controlled clinical trials and higher-quality guidelines are needed for the optimization of cell dosing.

5. MSC-based therapy for SCI

5.1 MSC transplantation is the most promising intervention for SCI

Unlike OA, which is an age-related degenerative disorder, SCI primarily affect young adults and is mainly caused by an external force (i.e. trauma) that disconnects the central and peripheral nervous systems, resulting in loss of

sensory, motor, and autonomic nerve functions below the level of the injury [92]. The average age of injury was approximately 43 years old in 2014 [93] and since that time it has tended to increase [94]. Worldwide the number of new SCI cases is about 250,000 to 500,000 per year and the prevalence rate in men is about four times that in women [95, 96]. In the United States, about 1,000,000 people suffer from SCI and more than 12,000 new cases occur every year [97]. According to the latest data published in *Lancet Neurology*, the number of SCI patients in China exceeds 3.7 million and the number of new cases per year is more than 90,000 [98]. Not surprisingly, SCI brings great economic hardship to individual patients, their families, and the healthcare system. Based on the location and severity of the traumatic injury, the lifetime cost of treating an SCI patient is about $1.5 to $3.0 million and the global annual economic cost is about $200 billion [96, 99, 100].

SCIs are difficult to heal and re-establishment of neuronal connections or neural circuits is rare [101]. SCI is divided into two stages of injury: primary and secondary. The former refers to the mechanical injury associated with spinal column fracture and dislocation, leading to spinal cord compression or fracture and vascular damage, the consequence of which is unpredictable and irreversible; while the latter refers to the response of the cells (and other biological reactions) to the primary injury, resulting in hemorrhage, ischemia, oxidative stress, inflammatory reaction, neural cell death, demyelination, and scar formation [92].

Based on time after injury, SCI consists of three phases. An *acute phase* (< 48 hours) is characterized by spinal ischemia, vasogenic edema and glutamate excitotoxicity, which trigger an overwhelming inflammatory response. This is followed by a *subacute phase* (48 hours to 14 days) characterized by neuroinflammation, mitochondrial phosphorylation, and the production of nitric oxide synthase (NOS), and a *medium/chronic phase* (> 14 days) characterized by apoptosis/necrosis, axon degeneration, axon remyelination and remodeling, and glial scar formation [92]. Consequently, there are three distinct histological compartments formed in SCI lesions, including a non-neuronal lesion core, an astroglial scar, and a spared reactive perilesional neural tissue [102]. Because of this histological pattern, the newly regenerated axons bypass the injury site, resulting in abnormal synaptic growth and limited functional recovery [102]. As a result of these pathological processes, a major principle for the effective intervention in SCI should focus on neuroprotection and regulation of neuroinflammation in the acute phase, promotion of angiogenesis and nerve regeneration, with suppression of scar formation in the subacute phase, and reconstruction of neural circuits, followed by recovery of neural function, in the chronic phase. At present, conventional therapies, which target each phase of SCI, have less efficacy at promoting a functionary recovery, resulting in a considerable number of side effects. For example, high-dose methylprednisolone (MP) is widely used to treat acute SCI, which mainly reduces inflammation to minimize damage caused by the secondary injury[103]. However, the efficacy of MP in treating SCI is controversial, serious side effects including gastrointestinal hemorrhage and respiratory, urinary tract, and wound infections, are of deep concern [104].

Compared with drug treatments, that often target a single signaling pathway and are unable to adapt to differences in the local microenvironment, transplanted MSCs are capable of actively sensing the pathological/SCI microenvironment and can rapidly react to cues by targeting multiple signaling pathways simultaneously, which lead to immunosuppression, regeneration, and anti-fibrosis [105]. Specifically, the implanted MSCs primarily improve the host tissue microenvironment by releasing a variety of bioactive factors that regulate the inflammatory response, provide nutritional support, and promote axonal regeneration and nerve repair, thereby remarkably minimizing the secondary injury phase of SCI and promoting recovery of neural function. Overall, MSC-based therapy has the potential to provide the most effective treatment for SCI with minimal side effects. In the following sections, we describe the properties of MSCs and discuss the various phases of SCI where these cells may be able to reverse (or ameliorate) the disease process.

5.2.1 MSCs Play a Role in Anti-inflammation

In the acute phase of SCI, blood-derived immune cells (e.g., neutrophils, myeloid monocytes, and lymphocytes) and necrotic tissue in the spinal cord produce a strong inflammatory reaction with increased levels of pro-inflammatory cytokines (e.g. TNF-α, IL-1α, and IL-1β) [106, 107], which induce migration of microglia and macrophages to the site of injury, followed by swelling and compression of the spinal cord, forming a vicious cycle [108]. MSCs are able to secrete IL-4, IL-13 and chemokine (C-C motif) ligand 2 (CCL2), which inhibit microglia activation, reducing the production of nitric oxide (NO) and promoting macrophage polarization to the M2 state (reducing M1 polarization), thereby decreasing the release of reactive oxygen species (ROS) and other inflammatory factors (e.g., IL-1α, IL-1β and TNF-α) [109, 110]. In addition, MSCs can also inhibit the activation of NLRP3, a component of the inflammasome, which reduces the release of pro-inflammatory factors (e.g. IL-1β & IL-18)[111, 112].

5.2.2 MSCs Protect the Cells from Apoptosis

In the subacute phase of SCI, nerve damage results in the production of increased intracellular calcium (i.e., Na^+ and Ca^{2+} flow into and K^+ flows out of the neuron), which activates calcium-dependent proteases (e.g., calpain), leading to deleterious changes in mitochondrial function, and eventually apoptotic neuronal cell death [113]. The debris generated by this process is subsequently removed by phagocytes, which release ROS, resulting in delayed necrosis and apoptosis through DNA damage and protein and lipid oxidation byproducts. A secondary process during this phase is the increased release of excitatory neurotransmitters (e.g. glutamate and aspartate) by neurons into the site of injury and eventually the circulation [109-112]. This high concentration of glutamate (and aspartate), which activates excitatory neurotransmitter receptors, creates a cytotoxic post-injury environment, resulting in further inflammation, scar formation, and the death of oligodendrocytes [114]. Paradoxically, excitotoxic levels of glutamate also activate adult spinal cord ependymal-derived neural stem/progenitor cells (epNSPCs) through calcium-permeable alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (CP-AMPARs) to promote epNSPC proliferation (via pCREB) and induce astrocytic differentiation (via upregulation of Hes1) [115]. This suggests that successful treatment of SCI may require tight control over glutamate levels. Interestingly, the MSC-secretome has been shown to support neuroblastoma cell survival in the presence of glutamate through the inhibition of neuron N-methyl-D-aspartate (NMDA) receptors [116-119]. In addition, other studies have shown that MSCs are able to protect neurons from glutamate injury by downregulating the production of growth-associated protein-43 (GAP-43) [120].

5.2.3 MSCs Have Anti-fibrotic Properties and Promote Axonal Regeneration

During the chronic phase of SCI, the mature lesion is surrounded by an astrocyte boundary that creates a cyst/cavity, containing extracellular fluid, macrophages, and cell debris [121]. This structure, often referred to as an astrocyte scar, limits the spread of inflammation [122, 123]. However, the astrocyte scar contains a mixture of oligodendrocyte precursor cells (OPCs) that express chondroitin sulfate proteoglycan 4 (CSPG4), a molecule which inhibits axonal regeneration [102, 124, 125] Interestingly, transplanted MSCs have been shown to inhibit the astrocyte reaction and glial scar formation and coat the CSPG4 surface [126, 127]. In addition, transplanted MSCs secrete brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3), which promote axonal regeneration [128-130]. In relation to remyelination, MSCs have been shown to promote retention of the myelin sheath and increase the number of myelinated axons, mediated by an increase in the secretion of CCL2 [131]. Moreover, MSCs have also been shown to support the aggregation and proliferation of Schwann cells through the production of BDNF and VEGF, which induces remyelination [132, 133].

5.2.4 MSCs Promote the Differentiation of Neurons

Although MSCs generally give rise to mesoderm-derived cells, it is evident that MSCs can directly trans-differentiate into ectoderm-derived neurons [134]. In addition, it is also possible that the transplanted MSCs can activate endogenous neural stem cells to proliferate and differentiate [135]. Previously, it has been shown that the injection of human MSCs decreases inflammation and promotes proliferation, migration, and survival of mouse neural stem cells [68]. Moreover, other interventions, such as electrical stimulation [136], culture under hypoxic conditions [137], and induction with mannotriose [138], ATRA, or UDP-4 [139], have been shown to promote MSC differentiation into neurons. Pre-treatment of MSCs with Pulsed Electromagnetic Field (PEMF) stimulation provides a more effective therapy for SCI than MSC transplantation alone [140]. These data suggest that pre-treatment of MSCs to induce differentiation to neuro-progenitor cells, followed by transplantation to the site of injury, may increase the efficiency of MSC-based therapy for SCI.

6.0 Factors that Influence Clinical Results with MSC Treatment in SCI

Table 4 lists the top 16 clinical trials of MSC-based therapies for SCI, published in the peer-reviewed scientific literature as described above. Factors that affected the results include the source of cells (tissue and donor origin), culture conditions for expanding the cells *in vitro*, routes of transplantation, dose frequency, and phase of the disease. The table also lists the methods used to evaluate the improvement of each patient, including: American Spinal Injury Association (ASIA) (https://asia-spinalinjury.org) sensorimotor score, bladder & rectal function, changes in ASIA Impairment Scale (AIS) grading [141], sensory evoked potential (SEP) and motor evoked potential (MEP), and, if performed, MRI studies. Based on the results summarized in Table 4 under “Main Results”, a “satisfactory” or “unsatisfactory” outcome was determined by the overall degree of motor and sensory improvement; it should be noted that functional recovery was not necessary. Moreover, in these studies it

is difficult to demonstrate that the degree of recovery was specifically contributed by cell therapy or was the result of a natural healing/reparative process due to insufficient sample size and lack of an untreated control group.

The major factors that may influence the efficacy of MSC transplantation in SCI are discussed below in the following sections.

6.1. Influence of cell source

The MSCs used in the 16 clinical trials listed in Table 4 were derived from three main sources: bone marrow (BM), adipose tissue (AD) and umbilical cord tissue (UC). Although these three types of cells are very similar in cell morphology, tri-lineage differentiation capacity, and surface marker expression [142], they are known to have different proliferation rates, immunogenicity, and immunosuppressive properties [143]. Overall, there is a lack of data for patients treated with autologous UC-MSCs, while allograft rejection has been reported in subjects once the cells differentiate into mature cells [144]. In contrast, BM-MSCs and AD-MSCs do not proliferate as well as UC-MSCs [145], but they are easier to obtain from autologous donors and, as a result, there are less concerns about their immunogenicity and transmission of pathogens. Unfortunately, there are no parallel clinical trials that compare the efficacy of MSCs, from various sources, in treating SCI. In the SCI clinical trials that we identified (n.b., trial #15 in Table 3 evaluated two sources of cells, resulting in a total of 17 for this calculation), BM-MSCs were involved in 10 studies (10/17), six of which showed significant efficacy. UC-MSCs were selected in 5 studies (5/17), four of which indicated significant efficacy, while AD-MSCs were selected in 2 studies (2/17), and one study showed improvement. Thus, compared to BM-MSCs, UC-MSC transplantation appeared to have more of an effect on SCI. This effect may be due to the fact that it's easier to acquire an adequate quantity of UC-MSCs for multiple doses (note studies #5, #12, & #15 had satisfactory outcomes after multiple doses) and their relatively high capacity to induce differentiation [146], immunosuppression [147], growth factor secretion [148], anti-inflammation, and anti-apoptosis [149]. However, since there were only a small number of studies, without parallel controlled clinical trials for comparison, we cannot make any firm conclusions. Moreover, it should be noted that in study #13, eleven subacute SCI patients, treated with BM-MSCs combined with human autologous Schwann cells, achieved statistically significant improvements in both sensory and neurological functions [150]. Unlike the OA studies described above, the majority of SCI patients were treated with autologous rather than allogenic BM- or AD-MSCs. These results suggest that the effect of age on the quality/quantity of autologous cells was less of a factor in the SCI patients who were younger than in the OA subjects.

Table 4. Clinical Trials Using MSCs to Treat Spinal Cord Injury.

#	NCT #	Pub	# Patients / Aver. Age or Range	Cell Source	Culture Conditions	Route/Dose Frequency	Phase of Disease	Main Results	Out-come	Ref.
1	Unregistered	2006	2 / 20yrs	Auto. BM-MSC	Mesencult media	Blood vessel near injury site / Once	Later	Improved SEP, MRI, motor and sensory function.	S	[203]
2	Unregistered	2009	30 / 33yrs	Auto. BM-MSC	Media w/10% FBS	Intrathecal / Once	Mid-late	2 of 30 patients showed neurological improvement; 3 had improved bladder function; no changes observed on MRI and ASIA	U	[204]
3	NCT01274975	2011	8 /23-54yrs	Auto. AD-MSC	Media w/5% FBS	Cephalic vein / once	Later	1 of 8 patients had mild tactile improvement on the AISA score; 2 patients improved in needling sensation; no improvement in motor function; no change in MRI, SEP & MEP	U	[205]
4	Unregistered	2013	40 / 35yrs	Auto. BM-MSC	N.R.	Intrathecal / Once	Later	Improvement in spinal cord function, AIS classification, and ASIA sensorimotor score; some improvement in SEP & MEP; no significant changes on MRI.	S	[206]

5	NCT01393977	2014	34 / 35yrs	Allo. UC-MSC	Media w/10% FBS	Intramedullary / Twice (repeat @ day 10)	Later	Improvement in sensory, motor, muscular tone, and Barthel index.	S	[207]
6	NCT01325103	2014	14 / 35yrs	Auto. BM-MSC	Media w/15% FBS	Intralesional / Once	Later	Improvement in ASIA sensorimotor score and AIS score, but not pain scores (VAS and PRI)	S	[208]
7	Unregistered	2016	16 / 41yrs	Auto. BM-MSC	Media w/10% FBS	Intramedullary / Once	Later	2 of the 16 patients had neurologic improvement; 5 improved based on MRI, 4 had improvement in SEP; and 6 had improvement in MEP; Others are not.	U	[209]
8	NCT02482194	2016	9 / 31yrs	Auto. BM-MSC	10% human platelet lysate	Intrathecal / Thrice (repeat @ week 4 & 8)	Mid-late	No MRI imaging performed, prohibiting any conclusions other than that the procedure is safe.	U	[210]
9	NCT02570932	2018	11 / 45yrs	Auto. BM-MSC	Media w/10% FBS	Intrathecal / Thrice (repeat @ month 3 & 7)	Later	ASIA sensorimotor score improved; spinal cord, sphincter, bladder and bowel, and sexual functions not improved.	S	[211]
10	NCT02510365	2018	2 / 29yrs	Allo. UC-MSC	Media w/serum substitute	Intramedullary / Once	Acute	Improvement in sensory, motor, bladder, and bowel functions, AIS classification, SEP, and MEP.	S	[162]
11	NCT03003364	2021	10 / 33yrs	Allo. UC-MSC	Media w/20% human serum B	Intrathecal / Once	Later	Only showed improvement in right-side pinprick sensation, but not in left pinprick sensation, bilateral mild tactile sensation, movement, anorectal function, and urodynamic scores.	U	[212]
12	NCT02481440	2021	41 / 38yrs	Allo. UC-MSC	Media w/10% human platelet lysate	Intrathecal / 4 times (repeat @ month 1, 2, & 3)	Mid-late	ASIA and IANR-SCIFRS total scores were statistically increased compared to baseline (ie, improved pinprick, light touch, motor & sphincter scores). Muscle spasm, autonomic system, bladder/bowel function, RUV, and MRI showed significant improvements. Sub-group analysis showed UC-MSC transplantation improved overall neurological function.	S	[213]
13	Unregistered	2021	11 / 29yrs	Auto. Schwann cells +BM-MSCs	DMEM/F12 w/10%FBS (cells washed & suspended in saline prior to injection)	Intrathecal / once	Mid	Sensory and/or motor improvement was evident in 9 out of 11 patients; however, none showed an alteration in AIS grade from A to other grades. Per SCIM-III assessment, 8 out of 11 patients showed some degree of functional recovery. The most remarkable	S	[150]

								positive, subjective improvements were in trunk movement, equilibrium (standing/sitting), bladder/rectal filling sensation, and ability to voluntarily void.		
14	Registered in Japan (JRCT10802 24764)	2024	10 / 49yrs	Allo Muse cells (CL2020)	Proprietary method (Life Science Institute, Tokyo)	Intravenous / once	Early (Frankel B1/B2)	ISNCSCI motor score, activities of daily living, and quality of life were significantly improved compared to before treatment with CL2020. No safety concerns were identified.	U	[214]
15	NCT04288934	2024	11 / 36yrs (Group A)	Auto. BM-MSC	Media w/10% FBS	Peri-lesional (once), followed 4 wks later by 3 intrathecal injections (1/month)	Later	ASIA scores improved after 1 year and continued to improve after 2-3 years. Both treatment groups showed similar levels of improvement	S	[215]
			9 / 39yrs (Group B)	Allo. UC-MSC	5% human platelet lysate media	Intrathecal, 3 injections (1/month)				
16	NCT03308565	2024	10 / 35yrs	Auto. AD-MSC	5% human platelet lysate media	Intrathecal / once	Mid-late	ASIA sensorimotor scores were improved in 7 out 10 patients over the 2 years of follow up; no improvement in MRI after 1 year	S	[216]

Sixteen clinical trials were identified and evaluated the safety and efficacy of MSCs for treating SCI. Factors that were followed in all of the studies included source of the cells (donor and tissue origin), culture conditions for expanding the cells, routes of transplantation, dose frequency, and phase of the disease. Methods used to monitor each patient's progress included the American Spinal Injury Association (ASIA) sensorimotor score, bladder & rectal function, changes in ASIA Impairment Scale (AIS) grading, sensory evoked potential (SEP) and motor evoked potential (MEP), and, if performed, MRI studies. Outcome of treatment was measured by overall degree of motor and sensory improvement (ASIA and AIS scores) and scored as "Satisfactory" if an improvement was seen with treatment or "Unsatisfactory" if no improvement was found or the patient's condition worsened.
Abbreviations used in the table:
AD: Adipose tissue-derived; **Allo**: Allogeneic; **ASIA**: American Spinal Injury Association; **Auto**: Autologous; **BM**: Bone marrow-derived; **IANR-SCIFRS**: SCI Functional Rating Scale of the International Association of Neurorestoratology; **ISNCSCI**: International Standards for Neurological Classification of Spinal Cord Injury (version: 1992); **Muse cells**: Multi-lineage differentiating stress enduring cells; **NCT #** = ClinicalTrials.gov ID; **Pub** = Publication date; **SCIM-III**: Spinal cord independence measure; **UC**: umbilical cord-derived

6.2. Culture conditions used to expand MSCs

Prior to transplantation, MSCs must be expanded to attain the number of cells needed to meet clinical demand. The culture conditions used during this process have an important effect on MSC properties including proliferation and differentiation capacity. Previous studies have shown that serum-free media are more conducive to maintaining the original characteristics of the cells, while promoting cell proliferation, than media containing conventional fetal bovine serum (FBS) [151, 152] Unfortunately, only a few of the studies identified in Table 4 used alternatives to FBS, such as human serum media, human platelet lysate media, serum-free media containing substitutes, and MSC-specific Mesencult media for expanding the MSCs. In the 16 studies, 1 did not specify culture conditions (trial #4), 9 used FBS- or human serum containing media, 4 used platelet lysate, and 3 used serum substitutes. Although there was wide variation in cell efficacy, the serum-free media (company undefined + human platelet lysate + serum substitute) appeared to be slightly superior (5/8) to conventional FBS media (5/9) in terms of producing MSCs that were efficacious in treating SCI. In fact, UC-MSCs cultured in FBS media had a higher percentage of senescent cells than those cultured in serum-free media [153]. In addition, the concentration of VEGF-A secreted by UC-MSCs cultured in serum-free media was significantly higher than that of cells cultured in media containing FBS [153]. Moreover, the proliferation and immunosuppressive potential of UC-MSCs cultured in the serum-free media were also higher than in the FBS group [154]. It should be noted that the serum-free media mentioned here does not refer to media lacking all of the nutrients typically found in serum, but contains combinations of cytokines, growth factors, hormones, etc., since the cells are more sensitive to their microenvironment under serum starved conditions [155].

Based on these results, serum-free media should be given priority for cell culture expansion.

6.3 Influence of transplantation route on the efficacy of MSC treatment of SCI

MSCs are routinely administered locally or systemically (e.g. intravenously [i.v.]). Local delivery of MSCs for treatment of SCI patients can be performed by either an intramedullary or intrathecal route. Many animal studies have shown that i.v. [130, 156], intraperitoneal (i.p.) [130], and intramedullary or intrathecal administration result in the repair of a variety of spinal injuries [157]. Moreover, animal experiments have demonstrated that local administration appears to produce superior therapeutic effects compared to i.v. administration [157, 158]. However, there are no parallel comparison clinical trials showing which route of delivery produces better therapeutic effects in humans. In Table 4, 1 study (#1) employed vascular injection at the injury site and the therapeutic effect was good; 1 study (#3) injected through the cephalic vein and another study (#14) used intravenous injection and both resulted in a poor treatment effect; 10 studies used intrathecal administration with 7 producing good results; 3 studies used intramedullary administration with 2 producing very good results; and lastly, 1 (#6) study used intra-lesional injection and produced a good result. Based on these results, it is uncertain which transplantation method is most effective, but it appears that the efficacy of local injection may be better than i.v. injection. To address whether intramedullary injection or intrathecal injection is preferable, the above-mentioned clinical trials do not provide a definitive answer. However, some studies have indicated that intramedullary injection may cause secondary injury; moreover, intramedullary injection is difficult to use in the case of a spread lesion or multi-focal SCI [159], while intrathecal injection does not present these issues [160]. However, intrathecal injection must be performed with caution as fluid movement is likely to decrease the number of cells reaching the site of injury [161]. Although studies have shown that MSCs will migrate to the site of injury after intrathecal injection [157], a decrease in the number of cells is inevitable. To enrich MSCs in the lesion site, biological scaffolds have been proposed because they promote retention, integration, and differentiation of MSCs at the site of injury [162]. Previous studies have shown that transplantation of stem cells, carried by biological materials (e.g., a gelatin scaffold or 2-hydroxypropylmethacrylamide-based hydrogel), are able to effectively promote recovery after SCI [163, 164]. This beneficial effect is due to the increased survival and enrichment of MSCs on the scaffold [165, 166]. In future clinical trials, we recommend co-transplantation of MSCs with biomaterials, which may produce better results than simple intramedullary or intrathecal transplantation.

6.4 Influence of MSC transplantation frequency on treatment success in SCI

The disease course of chronic SCI is often long and a single dose of MSCs may be insufficient to achieve a curative effect. However, few clinical trials compare the effect of single versus multiple transplants. Among the 6 clinical trials in Table 4 which used multiple local transplants, 5 showed satisfactory outcomes; in the 8 trials that used a single local injection for transplantation, 5 produced satisfactory outcomes. These data suggest that the efficacy of multiple transplants of MSCs may provide a better option than a single dose. As mentioned above, injection of MSCs into the cerebrospinal fluid leads to a reduction in the number of MSCs at the site of injury [167]; moreover, even if MSCs successfully reach the injury site, some cells will spontaneously die due to exposure to phosphatidylserine (PS) or they may be short-lived due to the microenvironment [167, 168]. Due to these factors/conditions, an increase in the frequency of transplantation might be a viable solution. Unfortunately, there are no reports that directly compare the therapeutic effects of single versus multiple transplantation, and this is an area where additional research is needed.

6.5 Influence of disease phase on treatment success in SCI

Different phases of recovery/healing from SCI can affect the survival of transplanted cells and/or secretion of trophic factors. A profound manifestation of the acute phase of SCI is inflammation. At this stage, MSCs can respond to the local environment (or microenvironment) by producing either pro-inflammatory or anti-inflammatory factors [169]. Some studies have shown that MSCs transplanted during the acute phase can have dramatic therapeutic effects by inhibiting inflammation [170]. However, other studies have shown that the pro-inflammatory microenvironment (rich in TNF-α) during acute injury impairs MSC survival and other important functions such as the production of exosomes, containing microRNAs (miRNAs), which direct angiogenesis [171-173]. Other researchers suggest that the sub-acute SCI microenvironment may be more conducive to MSC survival and axonal regeneration [174]. However, there is no unified understanding of when MSC transplantation works best during the different phases of SCI healing. According to the clinical trial data that we reviewed (Table 4), almost all of the studies (14/16) selected the sub-acute (i.e. middle to late) phase for cell

transplantation; 9 studies showed that treatment during this phase was effective, while the other 5 studies showed that treatment was ineffective. Only one study (#10) with two patients provided UC-MSC treatment during the acute phase and showed that MSC therapy was effective. Although most studies currently recommend transplantation in the sub-acute phase, MSCs have anti-inflammatory effects suggesting that they might be able to repair the microenvironment and reconstruct neural circuits during the acute phase of healing. The lack of information regarding the use of MSCs in the acute phase of SCI is likely due to the short amount of time available to prepare and administer the cells. Ideally, MSCs need to be administered multiple times to treat different phases of SCI.

6.6 Patient variation influences the effect of MSC treatment of SCI

Previous studies have shown that the host immune response in SCI has a negative effect on both the survival of MSCs [175] and their ability to inhibit the immune response [176, 177]. However, more research is needed to determine whether differences in patient immune response play a role in treatment efficacy and outcome.

According to the American Spinal Injury Association Impairment Scale (AIS) [143], SCI is classified into 5 levels, based on severity, using an A to E grading scale, with A being the most severe (i.e., no preservation of motor or sensory function in the sacral segments S4-S5) and E being the least severe (i.e., motor and sensory function are normal). Studies have shown that AIS grade A patients have a better response to MSC transplantation therapy than patients with AIS grades B, C, or D [178]. This means that MSC transplantation provides more benefits for subjects with more severe SCI.

Most comorbidities, such as diabetes, will affect the surgical management of SCI [179]. However, little attention has been paid to whether these comorbidities affect the efficacy of MSC transplantation. Moreover, complications associated with SCI, such as pressure ulcers, pulmonary infection, urinary tract infection, and venous thromboembolism also need to be evaluated to determine whether they have an effect on MSC treatment efficacy.

According to clinical experience and previous statistical analyses, age, etiology, and surgical intervention all significantly affect the length of stay in the hospital [180], suggesting that these factors not only influence the efficacy of conventional treatment but cell transplantation as well. This is especially important for *autologous* MSC transplantation, since patient age and medication usage may directly affect the quality of transplanted cells [58].

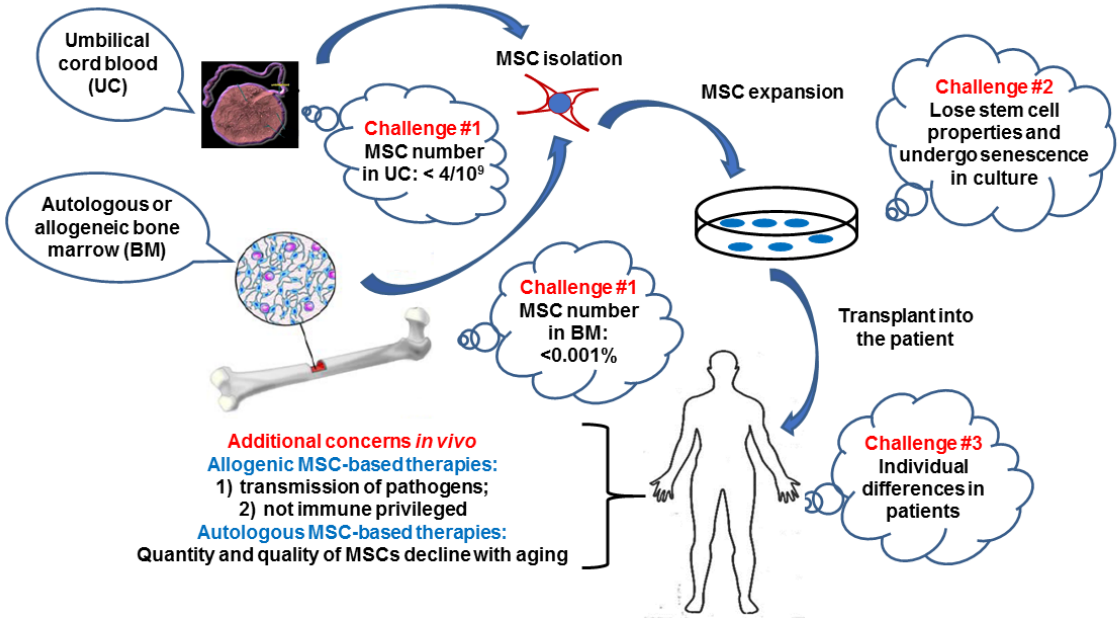

Figure 2. A graphical abstract showing the important factors that cause inconsistent results in MSC-based therapies.

The number of transplanted cells has to be considered as a critical factor influencing the results of MSC treatment of SCI. If the number of MSCs is too low, a therapeutic effect may not be achieved, and if the number of cells is too high, there is a risk of tumorigenesis. Prior studies have shown that after the number of transplanted cells exceeds a certain threshold, the number of surviving cells does not increase accordingly [181]. A meta-analysis of animal studies has shown that transplantation of a high-dose ($\geq 1 \times 10^6$) of UC-MSCs is superior to that

of a low-dose ($<1\times10^6$) [182], but studies in humans have failed to confirm these results due to the limited number of human clinical trials. Although there is no widely accepted dose (i.e. number) of transplanted cells needed to achieve efficacy in SCI, the number of transplanted cells commonly used is in the range of one to ten million. Clinical trials to optimize the number of cells needed to reliably achieve efficacy in SCI are needed.

7. Conclusions

By reviewing the ClinicalTrials.gov database, we found ~1,600 clinical trials that employed MSC-based therapies for over 108 different diseases but unexpectedly only 7% of these studies reported results (Table 1). For many, safety was the primary endpoint, while efficacy was not convincingly demonstrated. In this narrative review, we discuss critical factors in clinical trial design that may cause inconsistent outcomes and then propose how this information can be used to more predictably achieve the goals of personalized or precision medicine with MSC-based therapies.

We determined that OA and SCI were the most common diseases treated with MSCs and reported the most complete set of data for analysis. These two diseases are very different in terms of etiology (OA, predominately idiopathic, but some post-traumatic, versus SCI, traumatic injury) and the populations affected (OA, predominately older females vs. SCI, young males). Nevertheless, they highlight a wide variety of clinical factors, discussed in this review, that need to be considered when designing a clinical trial aimed at developing a personalized MSC-based therapy (see Fig. 2).

Since the number of MSCs in tissues is low, they need to be sub-cultured to expand the number of cells available for use in clinical applications. As discussed in this review, different laboratories expand their MSCs using a variety of culture conditions, resulting in significant differences in the quality of MSC populations. This is especially true with current TCP-based systems where MSCs lose their self-renewal and differentiation capacity over time in culture [16, 18], which impairs therapeutic efficacy. In addition, the response of individual patients to transplanted MSCs varies due to differences in age, sex, heredity, use of medications, stage of disease, etc. Over the last 10 years, MSC "immune privilege" has been challenged since mounting evidence suggests that allogenic MSCs elicit an immune response that leads to rejection of the transplanted cells [63, 183]. Importantly, the favorable clinical outcomes observed with allogenic MSC therapies are primarily due to the production of trophic factors by the MSCs shortly after infusion, resulting in a so called "hit-and-run" effect [183], while there are few reports indicating that the newly formed tissues *in vivo* are directly generated by the transplanted allogenic MSCs [67].

All of the issues discussed above are very challenging to incorporate into the design of a clinical trial because the number of patients (i.e., sample size) is limited, which makes it impossible to compare all of the possible variations in transplanted MSCs (e.g., different sources, doses, and frequency of administration, etc.) in a single clinical trial. In addition, the ethical guidelines/regulations that need to be followed when conducting human subjects research (e.g., randomized trial design with untreated control groups) are extensive. Moving forward, we must be more focused and develop standardized methods for preparing high quality MSCs, dosing schedules which are disease- and disease-stage specific, etc. We propose that the establishment of autologous personal stem cell banks may be an essential component for achieving success with MSC-based therapies. These repositories could be established during middle age (e.g., 30-45years old), while MSCs can be obtained that still display their youthful properties. For patients who are older (e.g., older than 65 years of age), their aged MSCs could be restored by culture on "young" ECM (i.e., ECM produced by stromal cells from young donors) as we previously described [58, 63]. In this case, large quantities of high quality autologous MSCs could be rejuvenated for immediate use or stored in a personal stem cell bank for future use when needed.

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Authors' contributions

SL, CZ, WW, WA, ZL, HZ, and XK collected information from the databases, designed the initial versions of the tables and prepared an initial draft of the review; *DDD* prepared a revised draft of the tables, prepared the figures, and wrote the penultimate draft of the review; *SF and XDC* conceived the idea for the review, curated and edited the penultimate and final versions of the review and figures/tables, and provided funding. All authors have reviewed and approved the final submitted version of the review.

Availability of data and materials

All data generated or analyzed during the current study are included in the article. Questions can be forwarded to the Corresponding Authors.

Competing interests

Dr. Chen is a Board member and shareholder in StemBioSys, Inc (San Antonio, TX). All other authors have no financial or competing interests to declare.

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